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Modern Trends in the Population Genetics of Man*

THERE HAVE BEEN many factors which have influenced our thinking on population genetics over the past ten or fifteen years. The term "Population Genetics" still connotes a largely theoretical subject. Chapters with such a heading in textbooks tend to deal with the hypothetical distribution of genes and traits in populations as determined primarily by Mendelian segregation and modified by factors such as fresh mutations at varying rates, selection in various degrees against different genotypes and different intensities of inbreeding in populations of finite size. The enormous complexities introduced by even these variables limit most of the theory developed to situations at single loci being considered in isolation from the whole genome.

The brilliant theories developed by Fisher, Haldane and Hogben in this country and Sewell Wright in the United States have been of the greatest value in advancing genetical thought and in stimulating further work. Over the years they have been vindicated by work on the population genetics of blood group gene systems. Indeed, they continue to mould the form of all planned observation in human genetics.

However, these theories, although valid when the strict conditions for their application are present, have severe limitations and can easily be misused even when considering what are probably single gene determined harmful traits in man. When we come to consider traits which, although not inherited by a simple mechanism, have some genetical component in aetiology and which are both more numerous and of greater social importance in man; then often only vague, complex and ill-defined hypotheses are available to be put to the test by planned observation in populations. It has to be remembered that such complexly inherited traits are more numerous and, on the whole, more severe in total effects on individuals and populations than those simply inherited. Therefore, from a medical point of view, it is important that their aetiology should be understood. The large range of ill-understood developmental anomalies and of premature degenerative processes with genetical components in aetiology form an impressive proportion of all wastage of human life at the present time.

Advantages and Disadvantages of Man as a Subject for Genetical Study

Before considering current preoccupations in human population genetics it seems well to recall some of the advantages and disadvantages of man as an organism for genetical study, for it is still sometimes assumed that the limitations of study of man are such that human genetics is a kind of poor cousin of experimental genetics, and perhaps even a rather dilettante occupation.

Some Advantages of Man

It is interesting to remember that following the pioneer papers of Haldane[2] and Penrose[1] there was a period of over ten years before a spontaneous mutation rate estimate was available for any vertebrate except man. At the present time estimates are available for some twenty autosomal dominant and a number of sex linked recessive genes in man. Further, these estimates are based, not only on the findings in free living populations in a manner quite impossible in experimental genetics, but the sizes of the populations in whom these mutations have occurred are very much larger than those available in experimental work, even with fruit flies. Men have

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names and other identifiable characteristics which enable them to be traced. They know their close relatives—even if it is said to be only the wise who know their own fathers! Men can detect subtle differences in each other because they are studying their own species. Everyone can recognize hundreds of individuals only seen once before and subtle changes of expression such as fatigue are recognized in a way impossible if another species was being studied. There is only one species of man and all races can interbreed. Men live in a greater variety of environments than any other creatures. Perhaps as important, practically and potentially, is the very high degree of sophistication of techniques of investigation of disease which have been developed in modern medicine, permitting a unique range and precision of variation in man to be displayed. When new discoveries of medical importance are made, the intensity and high standards of work which follows make for accumulation of knowledge at remarkable speed.

The first concept of specific enzymic products of genes arose in man some fifty years ago with Garrod's concept of inborn errors of metabolism and it was only after thirty years that work on neurospora and subsequently in other fungi, moulds and bacteria gave practical demonstration of the importance of this theory and again revolutionized genetical thought. The discovery of blood group incompatibilities in man gave rise to the sophistications of modern blood group serology. More recently, haemoglobin and serum protein differences, and the situations at loci uncovered by drug sensitivities are not only opening up new vistas in human genetics but are stimulating an immense amount of experimental work. Surgical problems of grafting uncovered histo-incompatibility problems which have also stimulated brilliant experimental research. In turn, these experimental researches feed back to man and offer further opportunities in medicine and human genetics.

Now that advances in techniques have enabled us to study mammalian chromosomes, practical needs, sophistications of clinical diagnosis far higher in man than in any other organisms and previous knowledge of histopathological changes, have made for very rapid advances in understanding of chromosomal morphology in man and above all in facility of relating developmental anomalies to chromosomal aberrations. Far more is already known of these relationships in man than in any other mammal.

A criticism of human genetics has been its apparent preoccupation with the abnormal and perhaps particularly with the harmful traits which are, in sum, socially unimportant. This is a valid criticism but it is important to realize that the rare is usually simply inherited and available for study with our blunt tools, and that these are just the kinds of characters still used by experimental geneticists for most of their work. Most animals used in experimental genetics are killed long before they have time to develop the premature degenerative processes with hereditary associations which we are urged to study in man. Few counterparts to these complex processes have been recognized or adequately studied in animals. Human medicine enables us to identify the abnormal with so much greater precision than in animals. It is not surprising that a large amount of experimental genetics, now as in the past, concerns itself with abnormal traits quite parallel to those studied in man. The great majority of such clear-cut harmful traits are extremely rare in free-living populations. Only their introduction into laboratory and use for example as markers in experimental work makes them familiar, but how often do they occur in free-living populations?

It so happens that two classes of genes useful in animal studies appear to have few counterparts in man. The first is the relatively mild effect "recessive gene". Human single recessive genes are, with the exception of albinism and a number of eye traits, nearly lethal. Almost certainly a majority of what the experimentalists regard as recessives would be recognized in the heterozygote in man and so would be classed as dominants. The second is that we have no common easily recognized differences in man determined by single genes such as those determining coat colour in animals.

Some Disadvantages of Man

Enough has been said, I think, to show that human genetics has for many years repaid with interest its original debt to experimental genetics

and it is interesting to see, in papers in experimental genetics journals, how much in the way of inspiration and technique has derived from modern medicine and human genetics. It is foolish, however, to make such comparisons for any other purpose than to show that, as in the wider field, all biology and medicine are complementary to each other and are the strongly cross-fertilizing component parts of a larger discipline.

It is proper, therefore, to point, in turn, to the limitations of human genetics. The greatest of all is obviously the impossibility of planned breeding experiments affording the classical and basic tool of genetical analysis. This is not so serious in respect of balanced polymorphic loci where by definition the least common allele is not likely to be maintained at its observed or calculated frequency by any substantial contribution from mutation. In those balanced systems the least frequently occurring allele would perhaps occur in about 1 per cent of individuals in a given population. At this frequency, however, with patience, sufficient matings of appropriate kinds turn up in time to produce most, if not quite all, of the information needed for adequate formal analysis.

The impossibility of test matings is serious, however, in respect of the harmful effect mutant gene traits where fresh mutation frequency, although very low, has theoretically a simple relationship to the gene and trait frequencies in populations. Matings between persons both affected by the same trait are uncommon events but where they occur rarely, by chance or by social selection as in the case of deaf mutism, they tend to reveal what we know from experimental animals and suspect to be very common in man on other grounds, namely, that mutations at different gene loci or of different alleles can determine indistinguishable traits. Further we cannot adequately separate the two mechanisms as would be possible by genetical analysis in well studied experimental animals.

So we must qualify our optimism about the validity of mutation rates as estimated for man and realize that some—I am tempted to think practically all—are the expressions of fresh mutations occurring at different loci or to different alleles at one locus. The former is more devastating than the latter, particularly in the context of quantitative radiation estimates.

It is extremely important in view of these difficulties that, unless the human geneticist is dealing with characteristics assessed in the laboratory (and often even then), every possible effort be made to keep to the highest clinical standards. This does not involve relying entirely on the diagnosis of a clinician—for he will tend to equate heterogeneous traits for other reasons, e.g. response to treatment. Rather, it implies the need for the closest co-operation with clinicians and for them to be so genetically orientated as to be on the look-out for both clinical and genetical heterogeneity.

Single Gene Trait Studies in Man

Perhaps the simplest and most obvious opportunity in human population genetics is to study the pattern of distribution of traits which are the expression of single autosomal dominant or sex-linked genes in a defined population. This at its best involves "complete ascertainment" of all cases in a defined population, the word of necessity being used in the rather specific sense as identification of all characterized individuals, either in a series of births in a geographical area or in a population living in a defined area. The sophistications of "ascertainment" and their bearing on interpretation of findings are too complex to be dealt with here and it must suffice to say that we can never be sure that an ascertainment is complete, and that nearness to complete ascertainment and the methods to be employed will be different for every trait. Anything short of complete ascertainment introduces serious sampling doubts. Further, the work involved takes time and persistance; it is expensive, and it is dependent on achieving a high degree of co-operation with many people. Much work of this kind has been done, particularly in Sweden, Denmark, the United States and the United Kingdom, and as a result we have a series of estimates of different trait frequencies and mutation rates. It is at least reassuring to find that the order of magnitude of mutation rates for this class of gene estimated per gamete per generation in man is similar to that in other species and that for the same genes of this class estimates made by different observers in all the

countries mentioned are in substantial agreement.

There remains doubt, however, as to whether they really represent absolute rates for specific gene mutations, the sum of similar mutations at one locus or the sum of like-expression mutations at different loci. It must also be a matter of surmise whether mutation rates for this narrow class of genes, namely well known grossly harmful autosomal dominant and sex-linked genes, are representative of rates of mutation at other loci.

Nevertheless, estimates of spontaneous mutations so made are an essential part of the logic of the rather hazardous estimates which have been made of the effects of radiation on human heredity. Work of this kind must continue and much of the methodology evolved in these studies has other applications. In any event, so far as total detriment to a population is concerned from dominant or sex linked genes whose expression is marked enough and specific enough to detect, we can make reasonable estimates of the total harmful effects in terms of premature death and of disability.

When we come to consider autosomal recessive genes the position is very different. As I have already mentioned those recognized in man are all grossly harmful in their effects and most are, in the genetic sense, lethal. The summated frequencies of the recessive genes are far greater than the sum of the previous classes considered. Individuals homozygous for such genes and therefore showing the trait are fortunately very uncommon. Further, it is likely that there are many hundreds of such genes which are not recognized at all but which are grossly deleterious and lethal, or near lethal, to homozygotes. This is simply because the homozygotes arise so infrequently and most commonly only in one member of a sibship, that the aetiology is not suspected. Even if two sibs are affected with a new and strange syndrome it is impossible to be more than suspicious, as common environmental factors or multifactorial genetical causes can just as readily determine such a situation. It is highly probable if two sibs are affected and the parents are related, that a recessive gene is involved but what proportion of such cases are reported in the literature? Further, of those reported how many are so fully described that any subsequent examples of the condition arising can be identified with reasonable confidence?

The Importance of Harmful Recessive Genes

Ascertainment of recessive traits is on the whole even more difficult than for dominant autosomal and sex linked recessive traits. This is mainly because they are usually so lethal that few subjects are living at any one time. Even with complete ascertainment, and all evidence pointing to a one-gene-one-trait relationship, mutation rate estimates are at best hazardous. Any calculations have to make so many assumptions not susceptible to check, and other known variables such as the effects of relaxation of inbreeding cannot be expressed in quantitative terms because the relevant information just does not exist.

Always there has to be assumed that the heterozygote carrier is neither at an advantage nor a disadvantage in selection, that there is no gametal selection and that the gene is uniformly distributed in the population studied. Such assumptions can seldom be tested.

There is a large group of lethal recessive genes in man which determine traits having a frequency of between 1/100,000 and 1/20,000 births. As in the whole of these islands there are only just over a million births a year, it is clear that a high gene frequency in a geographical isolate, or in a group such as Irish emigrants to England who tend to intermarry, could account for many cases. Unthinking estimates of gene frequency in the whole population from the total trait frequency could be very misleading. Suppose in a population of 50 million people there were ten cases, then, if we assume that the trait frequency represents the chance coming together of two genes in the offspring of carrier parents in a population where the gene is uniformly distributed, then we have to assume that the carrier frequency in the population is just under 1/1,000, i.e. there were 50,000 carriers. However, all these cases could have occurred in a subpopulation of about 100,000 in whom the great majority of the genes in the population were concentrated. In that case the carrier frequency in the isolate would be about 1 in 50 and the total carriers about 2,000 representing in the whole population a frequency not of 1/1,000 but

of about 1/25,000. Recent work by our Chairman this evening, Dr. Cedric Carter, and Dr. Louis Woolf on the preponderance of phenylketonuric children attending Great Ormond Street Hospital who have Irish origins provide an excellent example of this type of phenomenon.

However, there can be little question that in total harmful effects of single gene expressions, recessive genes are of much greater importance than dominant or sex-linked genes and may approach those of more complex constellations of genes determining developmental and degenerative conditions. Further, any increase of mutation rates from radiation or otherwise would in time raise the frequency of these traits, in the same proportion as dominant or sex linked.

Consanguinity Studies

As so many individual recessive gene effects cannot be recognized, extensive use has been made in recent years of another approach, namely, the ascertainment of cousin marriages and the comparison with those of non-consanguineous marriages in respect of the number of pregnancies, the occurrence of single recessive gene traits, the losses *in utero*, the malformations in foetuses and those born alive and the subsequent mortality experience in the offspring.

It is not, I feel, being merely a carping critic to say that no investigation has been conducted in such a way as to give data worth serious quantitative consideration except that conducted by Schull and Neel[5] in Japan and even this inquiry could only consider such marriages when at least one pregnancy ensued and one mature child was born.

From all these inquiries there is no convincing evidence of a role of recessive genes in abortions or non-specific cause still births. Of course, there may be recessive gene determined very early embryonic deaths but there is no evidence on this point in man and a proportion of recessive gene determined abortions and still births could be present but not in numbers statistically significant.

Experimental geneticists always assume that some abortions, still births and some complete infertility are determined by single lethal mutant genes in man. Further, they tend to assume that they must contribute appreciably to these intrauterine losses and to complete infertility. It is, however, probably fair to say that at very most a few per cent of such losses are so caused, because not only studies of the offspring of related parents but of consanguinity in the parents of abortions and stillbirths fail to supply any supporting evidence for such a contention.[7] Indeed, in much animal work death *in utero* seems to be equated to "lethals" whether "point" or gene mutations or gross chromosomal aberrations. No doubt both mechanisms occur in man but they cannot account for more than a small fraction of losses. In regard to harmful visible effect genes there is sufficient evidence, however, to show that on average in some Swedish, American, British and Japanese populations every individual is the heterozygous carrier of, on average, between two and four genes, each individually of low frequency in the population, which would be grossly harmful in the homozygous genotype. There is also evidence for an excess of early mortality from all causes in the offspring. The Japanese data has also raised other extremely interesting questions about recessive genes or at least about the effects of inbreeding not related so specifically to genotype at a single locus.

Some recent data which we have collected in Oxford suggest rather strongly that recessive genes play no part, or at least no important role, in determining complete infertility in otherwise normal persons: of some 700 spouses to infertile marriages only five are the offspring of related parents.

A whole theory has evolved using terms such as a "load of mutations", and "lethal equivalents" meaning an effect determining in total the same number of deaths as a specified number of completely lethal recessive genes. The derivation of such hypotheses is, however, rather tenuous and may be regarded as part of the result of trying to find ways of expressing genetical situations in numerical terms for the purpose of trying, in turn, to get quantitative estimates of radiation damage in man. Such conceptions are immensely stimulating but there is some danger, as always when numerical estimates are made, that the very hazardous derivation may be lost sight of in the subsequent mathematics.

The Basic Conception of Population Structure Regarding Single Harmful Recessive Genes

The real crux of the matter revolves round whether in most recessive genes the heterozygote carrier is just a normal individual whose viability and fertility are in no way affected by reason of his carrying a harmful gene at one of a pair of specified gene loci. If this is the situation, then, providing we are reasonably sure that the gene is more or less uniformly dispersed in a population, we can estimate a gene frequency and a mutation rate. If, however, the heterozygote either has a greater or less total effective fertility than that prevailing in the population, matters are different. A very small variation—much too small to be detectable—could have an immense effect on gene frequency. We may say that providing a gene lethal in the homozygote has once become established in a population it can be maintained at a constant level by rather less than 2 per cent heterozygote advantage without any further mutations ever occurring. Conversely any heterozygote disadvantage of that order of size would determine very high mutation rates indeed for any of the well known lethal recessive genes in man. It is virtually impossible, in practice, to detect any increase or decrease of fertility of heterozygotes greater than, perhaps, 10 per cent, so that we are very much in the dark concerning the mechanisms which determine recessive gene frequencies in man. Further heterozygote advantage may operate *in utero*.

It must be remembered also that any preferential entry into zygotes of germ cells, with or without a particular gene-gametal selection, is known to occur in experimental animals and a possible example has been advanced in man.[6] Such mechanisms would have an effect as large as heterozygote selection value variation with 1 or 2 per cent departure from random, and therefore equal contribution to zygotes of alternative alleles segregating from a heterozygote parent.

Balanced Polymorphic Traits

Although considerable advances have been made towards recognition of heterozygote carriers of grossly harmful recessive genes none of these, except in sickle cell disease and thalassaemia, can be recognized with sufficient accuracy or facility to make them practical propositions for population studies.

There is, therefore, increasing interest in the mechanisms which determine balanced polymorphisms of traits such as the blood groups, haemoglobins and haptoglobins and the increasing number of single loci variations increased by study of drug sensitivities. An understanding of some of these mechanisms would be of the greatest value; the stimulation afforded to population genetics by the sickle cell malaria story has been very great indeed.

In others, a remarkable complexity of related factors have been uncovered. The proven associations of the ABO blood groups with disease, and others which may well be shown to be associated, are almost embarrassingly large, sufficient in too facile a fashion to explain the polymorphism.[4] When to these is added the rather suggestive undue proportion of ABO heterozygotes born which may be accounted for by preferential survival *in utero*, or may be explained by gametal selection, then the position regarding the ABO blood groups is indeed complex. The undue proportion of MN individuals could similarly be explained by one of these mechanisms.

We must therefore expect to see a great increase in family studies of such polymorphic traits—an even more laborious practical proposition than mere population distribution of genotype studies.

Study of Disorders with Ill-understood Hereditary Associations

Finally, bearing in mind the unique opportunities for certain aspects of population genetic research in man, particularly high diagnostic standards of complex clinical syndromes and the large populations which can be studied, there is plenty of scope for rather empirical collection of good data. Even if, in our present state of ignorance, we can hardly see what information we should collect because we have no adequate hypothesis to test, we can note variables of known biological significance such as parental ages, consanguinity, pregnancy order, age of onset, cause of disorder, patterns of familial incidence and so on and make full ascertainments in communities making proper family studies as

we progress. In this way data becomes available on which some kind of an hypothesis can be advanced and then in turn a more narrowly orientated investigation started.

There is such an immense amount of work to be done by people with special skills at all levels of genetical knowledge. For the practising clinician perhaps the most important dictum is Bateman's "treasure your exceptions". To recognize an exception or a curiosity, however, there must be some genetical knowledge and it should be remembered that clinicians are the first to see sick people. For the statistically minded there is so much we would like to know about the causes of death of people characterized in various ways, about the total reproductive performances of members of cohorts of both sexes and so on. Knowledge of medical genetics and techniques developed in epidemiology open plenty of avenues for interesting work. Some of the studies are entirely orientated by hypotheses whose theory is far from the original observations on which they were based. Others are orientated by hypotheses evolved from recent work and finally, as I have mentioned, there are areas in human genetics where neither experimental or theoretical genetics point very clearly a way to investigate. However, the steady accumulation of information proceeds apace. Already population genetics theory has been enormously influenced by phenomena defined in human genetics and this is only the beginning.

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